Spreadsheet That Shows *P*-Value Functions

To the Editor:

While visualizing the *P*-value function is desirable,[1] it cannot be done using standard statistical packages. I created a simple EXCEL 2000 spreadsheet to take 2 × 2 contingency table values, compute simple ratios as described in Modern Epidemiology,[2] and graph *P*-value functions for both the corresponding odds and risk ratios. The spreadsheet can be copied from *http://www2.utsouthwestern.edu/publichealth/Aragaki/Epitools.htm*, along with documentation. Perhaps it will aid in the instruction of epidemiology students.

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Breast Cancer Among Women Who Work at Night

To the Editor:

The recent case-control study by Hansen[1] investigated the linkage between female breast cancer and night work. The author reconstructed the employment histories of 7,035 Danish women with breast cancer back to 1964, and compared them with an equal number of controls. Hansen found an increased risk of breast cancer among female night workers (odds ratio 1.5), but we have some reservations about the study.

The classification of cases and controls into the night worker/non-night worker category was not based on an individual ascertainment of each woman's work history, but rather on her being in a trade in which at least 60% of women work at night. The use of this 60% cut-off point also excluded female hospital workers (principally nurses), who are the single largest group of female night workers in the population being investigated.[2]

The study did control for important confounders such as parity, socio-economic status and age at birth of first and last child. The authors did not have information on individual alcohol consumption.

Hansen states that previous descriptive studies have found a linkage between female breast cancer and night workers such as flight attendants and radio/telegraph operators. Flight attendants, however, are exposed to cosmic radiation, which may be a risk factor for female breast cancer.[3] Radio and telegraph operators are exposed to electromagnetic radiation, which again may be a risk factor for female breast cancer.[4] Thus, the observed increased risk of female breast cancer in these descriptive studies may not be primarily due to night work, but may be mediated by other risk factors.

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The authors reply:

Although most breast cancers appear to be attributable to environmental exposures,[1] little is known about specific causes for this disease. Therefore, it is important to conduct epidemiologic studies in order to test all biological plausible hypotheses. It has been suggested that light-at-night may cause breast cancer and other hormone-related tumours.[2] Despite the high prevalence of persons who work at night and therefore are exposed to light-at-night, no major study has investigated this hypothesis. As an initial step to evaluate an association between night work and female breast cancer, we used a comprehensive data linkage for this purpose, in which it was possible to control for the major confounder, i.e. the reproductive outcome.[3]

The strengths of our nationwide register linkage studies are their size and the lack of selection and information bias.[4] A major problem, however, is often the relatively imprecise available information on some exposures. In our attempt to classify workers with predominantly night work, we used the registered information of being employed over half a year in trades in which at least 60% of the women worked at night. Thereby we omitted a major group of hospital workers in which the proportion of night workers is 41%. Owing to our data linkage, the odds ratio for breast cancer among female Danish hospital workers is 1.2 (1.1–1.5), and among the major subgroup, the nurses, the OR is 1.3 (1.1–1.4). Thus, among these groups, which have a lower proportion of night workers than those in our recent study,[3] the increased relative risk of breast cancer further supports our hypothesis.

As suggested by O'Connell and Buttimer, women employed in some trades with predominantly nighttime work may also be exposed to electromagnetic or cosmic radiation, which may also contribute to breast cancer risk in our study. Further, confounders such as alcohol, use of oral contraceptives or a lower level of physical activity among the night-time workers may at least partly have contributed to their observed in-

creased risk of breast cancer, and should be considered in subsequent studies.

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Does Alcohol Increase the Risk of Preterm Delivery?

To the Editor:

Kesmodel *et al*'s prospective cohort study[1] found women drinking 10 drinks or more a week had a three times higher risk of preterm delivery compared with those drinking less than one. We recognize this is an important piece of research into a contentious area.

The authors concede that some under-reporting was inevitable. We suggest that further steps might have been taken to reduce this problem. At 16 weeks gestation, subjects were asked to fill in two questionnaires: one for the medical record, including questions on concurrent maternal drinking and smoking, and one research questionnaire. We suggest underreporting may have been more likely because alcohol and smoking questions were posed in the medical records questionnaire rather than the research questionnaire. Subjects may have felt more inclined to under-report when they knew the information would be available to health professionals managing their case, perhaps fearing the information could prejudice their future management.

The authors mention that interviews were conducted to assess the degree of alcohol intake under-reporting. They found a "slight tendency toward under-reporting in the questionnaire" that they do not quantify. Sixty-four women at 16 weeks and 50 women at 30 weeks had 10 or more drinks (the threshold for the negative effect on gestational age). In view of these small numbers reported for the high-risk group, we believe the authors ought to have quantified this under-reporting tendency.

It occurs to us that under-reporting of smoking habits could have also been a problem in this study because it would have made it difficult to adjust for smoking as a confounder. We suggest that smoking could have also been asked about in the interviews to assess the degree of under-reporting. Alternatively, could biological markers of environmental tobacco smoke, such as nicotine or cotinine levels in saliva, serum, or urine,[2] have been used as an objective maternal measure of smoking habits?

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The authors respond:

Kilduff *et al* suggest that underreporting is more likely in a questionnaire for the medical record than in a research questionnaire. For the period 1 February 2000 through 31 December 2000 we have collected both types of information: In the questionnaire for the medical record (Q_{MR}) we asked a single question comparable with that that used for the analyses of preterm delivery[1] ("How many drinks do you approximately drink *per week* now that you are pregnant (one drink is the equivalent of one [bottle of] beer, one glass of wine, or one schnapps)?"). The question did not specify subcategories of alcohol, and possible answers were 0; <1 drink/week; any whole number of drinks/week: 1, 2 etc. In the research questionnaire (Q_{RES}) we asked about average weekly intake of beer, wine, fortified wine and spirits, including strength of beer, and alcohol free beer and wine (subsequently coded as 0). Possible answers for each subtype of alcohol were as above. Intake of <1 drink/week was coded as a quarter of a drink/week. A total of 4,546 women returned Q_{MR}, of whom 4,411 had answered the question on alcohol intake, and 4,030 had filled in Q_{RES}. For 3969 women information was available for both instruments.

Mean difference between the two measures ($Q_{RES} - Q_{MR}$) was 0.1 drinks/week (standard deviation, SD = 0.4). Eighty-six percent of women reported the same intake in both questionnaires, 5% underreported, and 10% overreported intake in Q_{RES} compared with Q_{MR} (Table 1). Interestingly, the tendency toward underreporting in Q_{MR} compared with Q_{RES} was most evident at the lowest intake levels, and might be explained by the more detailed questioning in Q_{RES}. Further, women who had not filled in Q_{RES} were more likely to be abstainers (61% versus 46% as measured in Q_{MR}), and smokers (21% versus 13%) compared with women who had filled in Q_{RES}. So, in this case, one would have to weigh what little may possibly be gained by using information from Q_{RES} against this selection bias.

Comparing the data from the questionnaire for the medical record with information from a more extensive interview, where the same precategorized answers were used as those reported earlier,[1] 69% of women reported the same intake, 23% underreported their intake in the questionnaire compared with the interview (95% within one category), and 8% overreported (86% within one category).[2] In a later study we found that mean intake was 0.4 (SD = 1.2) drinks/week lower in the questionnaire compared with a two-week diary, and 0.3 (0.9)

TABLE 1. Agreement Between Two Measures of Alcohol Intake During Pregnancy (Drinks/Week): Questionnaire for the Medical Record (Q_{MR}) Versus Research Questionnaire (Q_{RES})

Q_{MR} (drinks/week)	Q_{RES} (drinks/week) 0	<1	1–2	3–4	5–9	10–19	≥20	Total
0	1598 (87.9)	214 (11.8)	6 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1819 (100.0)
<1	63 (4.1)	1364 (88.1)	103 (6.7)	17 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	1548 (100.0)
1–2	4 (0.8)	99 (20.0)	348 (70.2)	43 (8.7)	2 (0.4)	0 (0.0)	0 (0.0)	496 (100.0)
3–4	0 (0.0)	1 (1.2)	11 (13.4)	63 (76.8)	7 (8.5)	0 (0.0)	0 (0.0)	82 (100.0)
5–9	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	18 (94.7)	0 (0.0)	0 (0.0)	19 (100.0)
10–19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	3 (75.0)	0 (0.0)	4 (100.0)
≥20	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)
Total	1665 (42.0)	1678 (42.3)	469 (11.8)	123 (3.1)	29 (0.7)	4 (0.1)	1 (0.0)	3969 (100.0)

Numbers are number of women (row percentage). Aarhus, Denmark, 2000.

drinks/week lower compared with an average measure from an interview.[3]

With respect to information on smoking habits, measurement error of potential confounders may distort the results.[4] We have previously compared the prospectively collected information on smoking habits with retrospectively collected information from questionnaires and found no noteworthy differences.[5] Differences were independent of recall time and pregnancy outcome, including preterm delivery (mean difference between methods (current − retrospective): 0.17 cigarettes/day (−0.32, 0.65) for preterm versus term deliveries).[5] Interestingly, recall diminished with increasing alcohol intake, particularly for women smoking ≥10 cigarettes/day.[5] It may be that both measures were underreported compared with interviews. We have recently collected data that may shed light on this point (data not yet available for analyses).

Alternatively, measurements of cotinine in saliva,[6,7] serum,[8] or urine,[9] or of carbon monoxide in expired air[10] may be used as measures of smoking habits. It seems, however, that pregnant women claiming to be non-smokers may have high cotinine levels in serum and urine[8,11] (possibly because of exposure to passive smoking or denial of smoking status), and vice versa.[8,11] The findings of smokers with low cotinine levels suggest that because of intraindividual differences in cotinine concentrations in body fluids, a combination of self-reports and biological markers would be preferable.

We take this opportunity to note that there was a minor error on page 513, left column, last paragraph, third sentence in the original article.[1] The definition of a drink is the equivalent to 4 cL (centiliters) of spirits, not 4 mL as stated in the original.

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Urban Air Pollution and Lung Cancer in Stockholm

To the Editor:

In their recent article, Nyberg *et al.*[1] reported that urban air pollution increased the risk of lung cancer. While it is mathematically possible to perform the calculations as Nyberg at al.[1] have done, the inherent lack of precision and accuracy of the input data make it impossible to achieve the accuracy implied in the paper. The use of sophisticated statistical models can not reasonably change the crude input data to the level of precision reported.

Their exposure estimations were based on techniques conceptually similar to estimating individual exposures in an in-

dustrial setting. Nyberg *et al.*[1] used contemporary estimates of NO_2 and SO_2 emissions from vehicles and heating in atmospheric models to estimate concentrations at least 35 years in the past in regions as small as 100 meters squared. Their data are reported to the levels of 100ths of a $\mu g/m^3$, which translates to 10 parts per trillion (or 100 parts per trillion if they reported the means 1 decimal beyond the precision of their data). It is technically difficult even under experimental conditions to measure to 10 parts per trillion, which is the equivalent of 1 drop in a 1.8 km (1.1 mile) long train of tank cars. It is impossible in an observational study without any contemporaneous exposure measures to measure to a level of precision orders of magnitude greater than is possible with the best dispersion models under well-defined and ideal conditions.

It is tempting to equate the Nyberg *et al.*[1] individual-level exposure estimates with work place exposure studies, but there are important differences. Retrospective workplace exposures are usually based on measured exposures of some workers in a job for a defined work period, a process that makes estimates of cumulative exposure reasonable. An alternative estimation method is group-level exposure estimation in which a single measure is assigned to all subjects in an area or city. While the Nyberg *et al.*[1] approach is an improvement over group-level exposures, it makes the unwarranted assumption that the subject spends the bulk of his time outdoors within his 100 by 100-m grid. But, about 90% of the time is likely spent somewhere indoors where personal activities and indoor sources dominate.

Furthermore, the binary adjustments for occupational exposures used by Nyberg *et al.*[1] are crudely done and cannot reasonably account for these non-ambient exposures. The process divides the subjects into one group with additional exposures that overwhelm the ambient exposure being tested, and another group with an exposure range similar to the ambient exposure. The 'adjustment' for the difference in these two types of confounding exposure is inadequately attempted by adding a single value to the final effect estimates.

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Four of the authors reply:

Nicolich and Gamble have questioned the methodology used in our recent study.[1] Our exposure assessment did not use contemporary estimates of NO_2 and SO_2 emissions, but used reconstructed emissions in three retrospective emission databases, representing emissions in the 1960s, 1970s, and 1980s, respectively. These estimated emissions were then input into atmospheric models to calculate a geographical distribution of pollutants. More details of the method used can be found in a companion paper.[2] In the next step, our goal was not to measure absolute concentrations in regions as small as 100 meters squared, as Nicolich and Gamble suggest. Instead, we measured the *relative* variation across a large region (Stockholm County) with a resolution for concentration gradients of 100 meters squared. Our data were reported to 100ths of a $\mu g/m^3$ because the resulting estimated exposure was a continuous variable and cutpoints were determined by percentiles. To unequivocally state the cutpoints, as requested by the Journal Editors, it was necessary to use two decimals. Although two individuals on either side of a cutpoint are virtually indistinguishable, cutpoints at the group level are useful and quite valid for separating groups of exposed with different average exposures. In addition, we present analyses of continuous variables alongside the categorical analyses for a more complete picture. Similarly, while we appreciate the difficulty in measuring one drop in a train of tank cars, we were concerned chiefly with defining relative contrasts of exposure between individuals with regard to the pollutant in question, not with determining concentrations of the pollutant in relation to total air volume. In this regard, measurements to $\mu g/m^3$ or parts thereof are perfectly feasible and are routinely used in pollution monitoring.

We agree with Nicolich and Gamble that there are important differences between our individual-level exposure estimates and workplace exposure studies. One does indeed have to assume that differences in concentration at the place of residence represent differences in total exposure reasonably well. For many pollutants, such as NO_2 and fine particles, indoor concentrations reflect outdoor concentrations. Even for SO_2, we believe the interindividual differences in estimated outdoor levels at the place of residence are a reasonable proxy for interindividual differences in exposure. Many studies have also shown that stationary monitoring can represent the ambient exposure of individuals reasonably well because it is less influenced by very local sources than is the case in workplace exposure situations. Furthermore, nondifferential misclassification of exposure due to imprecise exposure estimation would tend to attenuate any association between a continuous exposure variable and disease, and we find no reason to believe that exposure misclassification differed between cases and controls in our study. Therefore, the lack of association with SO_2 may be questioned based on nondifferential misclassification, whereas for the association with NO_2 the main potential problem due to nondifferential misclassification is that it may be underestimated.

The occupational analyses and choice of variables are based on careful analyses outlined in another companion paper.[3] Adjustment for occupation using three specific dichotomous exposure variables and one more general variable produces a finely tuned occupational adjustment that we believe is quite adequate. Whether the exposure "overwhelms" the ambient exposure is not the point; the strength of occupational exposures as potential confounders in the ambient analysis depends on both strong association with lung cancer risk and close correlation with the ambient exposures, a situation that is unlikely for any of the occupational exposures studied. In addition, exploratory analyses showed that inclusion or exclusion of occupational exposures in the model had little influence on the risk estimates for NO_2.

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Congenital Malformations and Maternal Exposure to Glycol Ethers in the Slovak Republic

To the Editor:

We previously reported an association between occupational exposure to glycol ethers during pregnancy and the risk of congenital malformations from a study conducted in four European countries.[1] Since then, additional reports have appeared, some supporting these findings[2,3] but not all.[4] As part of the European Community Programme for Cooperation with Central and Eastern European Countries (PECO), we set up a similar case-control study in Slovakia to assess exposure to glycol ethers.

Twenty-six of the 69 maternity hospitals and obstetrical clinics in Slovakia agreed to participate. These participating institutions deliver 20,000 births annually (one-third of all births in Slovakia). During the data collection period (1995–1996), 196 mothers of live or stillborn babies with a major malformation or fetuses from therapeutic abortion were interviewed and included in the analysis, that is 65% of the number of eligible cases in these clinics. The majority (179) of cases were live births. For each case, we selected one control with no anomalies at birth, born after the case, in the same hospital or clinic. A refusal rate of up to 20% (varying by institution) was recorded for controls. Local physicians, using the study questionnaire, interviewed mothers of cases and controls at the clinic about various risk factors and obtained a detailed description of occupation at the beginning of pregnancy.

Slovak mothers reported exposure to various compounds that can contain glycol ethers, including cleaning agents, cosmetics, paints and varnishes, inks, dyes and glues, various solvents or degreasing agents and pesticides. Within these seven product families, two chemists (JF, SP), blinded to case status, assessed glycol ether exposure, using the subjects' descriptions of their job, information from the factories where the subjects worked, and records of the composition of chemicals from the Chemical Safety Centre and the Toxicological Information Center in Bratislava. The experts identified 15 women with potential exposures to GE: 2 industrial cleaners, 4 hairdressers, 2 women working with leather, 1 working with rubber, 2 electricians, 1 artificial flower dyer, 1 locksmith, and 2 foresters. For 11 women, the composition of the glycol ether compound was known: 7 contained ethylene glycol ethyl ether and 4 ethylene glycol butyl ether or its acetate.

TABLE 1. Odds Ratios* (OR) and 95% Confidence Intervals (95% CI) for Congenital Malformations Associated with First Trimester Exposure to Glycol Ethers, According to Group of Malformations (Working Mothers Only)

	No.	Exposed	OR	95% CI
Controls	131	5	1.0	
Cases	107	10	2.3	0.7–7
Cardiac anomalies	42	5	3.2	0.8–12
Endocardial cushion defects and septal defects	23	3	3.4	0.6–18
Anomalies of valves	7	1	6.6	0.5–89
Other cardiac anomalies	15	1	nc	
Musculoskeletal anomalies	20	0	–	
Central nervous system anomalies	20	2	2.7	0.4–16
Neural tube defects	16	1	nc	
Hydrocephalus	4	1	nc	
Cleft lip/palate	18	2	3.9	0.6–25
Cleft palate without cleft lip	7	1	7.7	0.6–103
Cleft lip with or without cleft palate	11	1	2.5	0.2–27
Digestive system anomalies	9	0	–	
Genital and urinary anomalies	13	2	2.9	0.5–18
Genital anomalies	3	0	–	
Urinary anomalies	12	2	3.0	0.5–19
Other anomalies	1	0	–	
Multiple anomalies	13	1	1.5	0.1–15

nc: The adjusted OR could not be estimated because the iterative computation does not converge; –: OR could not be computed because there were no exposed cases.
* Adjusted for maternal age at birth, socioeconomic status and residence, except for cleft palate without cleft lip, which is adjusted only for maternal age and residence.
NOTE: The number of malformations is greater than the number of cases because some infants had multiple anomalies.

The distribution of congenital malformations in each broad group of anomalies was very similar to those observed in our previous study. Odds ratios (ORs) for glycol ether exposure during the first trimester of pregnancy were estimated among working mothers for each subgroup of anomalies, adjusted for maternal age, rural residence and mother's socioeconomic status (Table 1). The overall risk of congenital anomalies was elevated (OR = 2.3), with a 95% confidence interval of 0.7–7.0. Risks exceeded one in all but two anomaly groups (musculoskeletal and digestive).

Among the 15 potentially exposed women, the experts put 10 (7 cases, 3 controls) into the highest exposure category. Among this high-exposure group, the OR for all malformations was slightly higher (OR = 2.7; 95% CI = 0.7-11). Malformation-specific ORs were increased with high exposure for all except cardiac anomalies (unchanged) and urinary anomalies (decreased).

This study in Slovakia found results similar to those in our initial study in Western Europe. The small sample size and low prevalence of glycol ether exposure (6.3 % of working control mothers, compared with 21% in our first study) prevent firm conclusions. Risk estimates increased among mothers with higher exposures, suggesting a dose-response relation. Although the range of occupations here obviously involved many chemical exposures other than glycol ethers, we found no other single chemical that was related to congenital malformations.

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Membership in Australasian Epidemiological Association

To the Editor:

I read with interest the recent paper on causal inference by Holman et al.[1] In their study, the authors mailed sets of 12 simulated scenarios to members of the Australasian Epidemiological Association (AEA) and asked them to indicate whether they were likely to attribute causality to the association described.

As current President of the AEA and as a participant in the study, I would like to point out an error in the authors' description of the membership policy of the organization, and therefore their description of the study population, as this may affect some readers' interpretations of the results.

The authors indicated that full membership in the AEA was granted after review by an election committee and that membership at the "associate" level was available for those who did not qualify for full membership. Although this was true in the early years of the AEA (which was formed in 1987), it has been AEA policy since the early 1990s that full membership is open to anyone with an interest in epidemiology. This includes epidemiologists and non-epidemiologists from a wide range of backgrounds. Our records indicate that the change to open membership was approved in 1992, well before the study that was conducted in 1997–1998 by Holman, et al.[1]

The authors also indicated that the study participants included epidemiologists in both Australia and New Zealand. Because of the history and structure of the organization, we maintain separate databases for Australian and New Zealand members, based on country of residence. Given the very small number of respondents (four) who reported New Zealand as their country of training (see Table 1 in Holman et al.[1]), I think the authors may have been using a list of Australian-based members, rather than a list of the total AEA membership.

While I don't think either of these errors detracts substantially from the value of this groundbreaking study, I thought it would be worthwhile to provide clarification. I found the study to be quite thought provoking and stimulating, and I look forward to more work in this area.

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Reference

1. A psychometric experiment in causal inference to estimate evidential weights used by epidemiologists. Epidemiology 2001;12:246–255.

The authors respond:

We requested a mailing list from the Australasian Epidemiological Association (AEA) of all members, but not associate members. We agree with Dr. Cunningham that the relaxation of AEA membership policy in 1992 should be noted, but that it does not detract substantially from the value of the study. Concerning the second issue, as the authors who dealt with the mailing list provided by the AEA, we can confirm that the list did, in fact, include individuals whose professional mailing address was located in New Zealand, such that we needed to arrange for international reply-paid envelopes.

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Pesticides and Fetal Death due to Congenital Abnormalities

To the Editor:

The recent case-control study by Bell *et al*[1] evaluated the risk of fatal congenital defects from pesticide exposure, expanding and refining a previous study.[2] Study subjects were classified as exposed if a pesticide application was recorded within a square mile area that included the woman's residence or, with lesser confidence, if an application occurred in adjacent square mile areas. This use of state-mandated reporting of pesticide

applications in California obviated concerns about recall bias that often plague case-control studies of pesticides. In addition, the authors' focus on applications during the critical weeks 3–8 of gestation added specificity to their analytic approach.

Pesticide exposure biomonitoring studies and spray drift models would suggest, however, that very few, if any, study subjects had the (appreciable) pesticide exposures ascribed to them. The most relevant research on this point comes from biomonitoring studies of farmers' families coincident with a pesticide application on their farms,[3] and a study of bystanders,[4] coincident to a residential pesticide application. The results of these studies show a moderate to high proportion of subjects with non-detectable values. As long as there was no direct involvement in the application, the remaining subjects tend to have extremely low values. Based on these studies, it seems unlikely that there would be appreciable exposure from a specific pesticide application in adjacent square mile areas or even within the same square mile area.

In a broader sense, for the exposure model used by Bell and colleagues to be valid, one must assume that pesticides travel fairly widely in the ambient environment in concentrations large enough to be teratogenic. If that had been the case, herbicides used in California during the study period would have harmed vegetation between the recorded application sites and the subjects' residences and the insecticides used would have harmed insect populations. Spray drift models (*eg*, AgDRIFT) based on cooperative research between industry and the Environmental Protection Agency predict that the concentration of pesticides drops off rapidly with distance from the point of application.[5] More detail about the distances between subjects' residences and specific pesticide applications would aid in the evaluation of this study.

Bell *et al* could evaluate their approach to exposure assessment in several ways: by looking for evidence of environmental effects implied by their exposure model; by employing pesticide drift models to assess the likelihood of exposure; or, best yet, by conducting a small biomonitoring study at the closest distances considered in their study. Such data would shed light on the validity of their reported findings.

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5. Teske ME, Valcore DL, Hewitt AJ. A review of ground sprayer data and a preliminary analytical model. American Society of Agricultural Engineers Annual International Meeting, July 2000, ASAE Paper no. 001112.

The authors reply:

Acquavella and Burns raise two issues regarding exposure assessment in studies of residential proximity to agricultural pesticide applications and birth outcomes: the magnitude of drift from pesticide applications to residential areas, and whether a biologically-active dose level would harm vegetation and insect populations. Several studies have shown that, when compared to the general population, individuals living near agricultural crops have an increased exposure to agricultural pesticides due to drift at the time of application.[1–3] These studies have measured detectable levels of pesticides in house dust from homes located within mile of agricultural crops. However, detection decreased as the distance between the homes and crops increased.

In our study, we assigned proximity to exposure by using the "TRS" (township, range, and section) from the USGS (US Geological Survey) to define a fixed unit of one square mile.[4] If a woman's residence was near the edge of the TRS in which she lived, and an application occurred near her home but in the adjacent TRS, then our narrow definition of exposure would classify her as "unexposed." Therefore, we used the broad definition, which included her TRS of residence and the eight surrounding TRSs, in order to increase the sensitivity of the exposure categorization. By using this definition, we could have misclassified some individuals outside the range of drift as exposed. However, given that nondifferential exposure misclassification tends to bias estimates toward the null, it is unlikely that the observed increase in risk was due to exposure misclassification. At the time of our study, we were limited to a resolution of 1 square mile. Recently, geographic-based exposure metrics have been developed that can be linked to the California pesticide use database in order to more precisely estimate the proximity of agricultural pesticide applications to residences.[5] These new methods could serve as valuable exposure assessment tools in future studies.

The authors also suggest that the validity of our exposure model is dependent upon having an environmentally relevant dose (*ie*, the insect population and vegetation between the application and residence would be noticeably damaged). Given that the agricultural pesticides are applied to crops in order to control for insects or weeds, we can assume that this criterion would be met for mothers living in very close proximity to agricultural crops. However, this criterion assumes that the biologically and environmentally relevant doses are equal. Several studies have shown that the risk of adverse birth outcomes (birth defects in particular) is a factor of both dose and fetal age at the time of exposure.[6–8] Thus, we cannot rule out the possibility that the environmentally safe dose is greater than the biologically relevant dose for a fetus, particularly when the exposure occurs during a vulnerable period of fetal development.

We agree with Acquavella and Burns that studies of residential proximity to agricultural pesticide applications would benefit from an improved measure of exposure. Nevertheless, our study represented a significant improvement in the exposure assessment over the majority of studies evaluating reproductive health effects of pesticides. Geographic proximity was not subject to recall bias, and gestational age at the time of exposure was known. As discussed above, methods that incorporate geographic mapping techniques in conjunction with pesticide application data have been developed that could improve the specificity of exposure classification. Finally, biomonitoring studies that characterize pesticide exposure due to drift, controlling for variability in wind and weather conditions, would lead to better understanding of environmental exposure to agricultural pesticides.

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Pesticides and Fetal Death due to Congenital Anomalies: Implications of an Erratum

To the Editor:

In a recent case-control study, we examined the association between residential proximity to applications of agricultural pesticides and late fetal death due to birth defects.[1] Elevated risks were observed for all five pesticide categories examined, with the greatest risk occurring when applications took place during the 3rd–8th week of pregnancy and within the same square mile as the maternal residence.

After publication, we determined that the pyrethroid categorization in our analysis was incorrect. The corrected pyrethroid category now includes the following pesticides: cypermethrin, pyrethrin, permethrin, fenvalerate, and flucythrinate.[2]

Fenvalerate and permethrin were the most highly used pesticides within the pyrethroid category, with 46 and 30 individuals, respectively, who were potentially exposed during the 3rd–8th weeks of pregnancy. Of the pesticides erroneously included in our original pyrethroid category, paraquat dichloride was the most highly used, with 34 individuals exposed during the same period. With the exception of piperonyl butoxide (22 exposed), fewer than 12 individuals were exposed to each of the non-pyrethroid pesticides.

To determine the correct associations for pyrethroids, *we repeated the* analyses with only the true pyrethroid pesticides. We also examined the risk associated with exposure to paraquat dichloride.

As previously described,[1] exposure was determined for three gestational time periods (1st–20th, 1st–13th and 3rd–8th weeks of pregnancy) and exposed women were compared to those not exposed to the class of pesticides being evaluated. A fourth exposure definition compared those exposed to specific pyrethroids during the 3rd–8th weeks of pregnancy with those not exposed to *any* of the pesticide classes during the same time period.

Within the same or eight surrounding Township, Range, and Sections (TRSs) (one square mile), the ORs for exposure to pyrethroids are larger in this new analysis, with ORs ranging from 2.2 (95% CI = 1.0–4.7) to 3.8 (95% CI = 1.6–9.1) for exposure during gestational weeks 1–20 and 3–8, respectively (Table 1). Risk increases as the time window for exposure narrows in on the period of organogenesis and also when the non-exposure category is restricted to those not exposed to any of the pesticide classes examined; analysis under these two conditions produces an OR of 4.9 (95% CI = 1.9–12.9)). The ORs in this new analysis are less stable, however, with the 95% CI width increasing substantially for all estimates. The associations

TABLE 1. Adjusted* Odds Ratios for Potential Exposure within the Same or Eight Surrounding Square Miles of the Maternal Residence for Pyrethroids and Paraquat Dichloride for Four Exposure Definitions

Exposure Definitions†	Pyrethroids		Adjusted		Paraquat Dichloride		Adjusted	
	Control	Case	OR	CI	Control	Case	OR	CI
Exposure A								
No	535	56	2.2	1.0–4.7	388	48	0.8	0.4–1.4
Yes	76	17			223	25		
Exposure B								
No	556	60	2.2	1.0–4.7	429	51	0.9	0.5–1.7
Yes	55	13			182	22		
Exposure C								
No	579	61	3.8	1.6–9.1	502	55	1.4	0.7–2.7
Yes	32	12			109	18		
Exposed D								
No	343	30	4.9	1.9–12.9	330	30	1.8	0.9–3.9
Yes	32	12			109	18		

* All models adjusted for maternal age and county.
† Exposed to specified class versus not exposed to same class during:
Exposure A: the first 20 weeks gestation
Exposure B: the first 13 weeks gestation (first trimester)
Exposure C: the 3rd- to 8th-week period of gestation
Exposure D: exposed to specified class between 3–8 weeks gestation versus not exposed to any of the five classes during the 3rd- to 8th-week period of gestation.

are stronger when analyses are restricted to pesticide applications within the same square mile as the maternal residence, although small numbers prevent examination of exposure during the 3rd–8th weeks of pregnancy.[2]

In contrast, potential exposure to paraquat dichloride in the same or eight surrounding TRSs show no association, with ORs of 0.8 (95% CI = 0.4–1.4) for exposure during the first 20 weeks and 0.9 (95% CI = 0.5–1.7) for exposure during the first trimester of pregnancy. The risk increases, however, when exposure occurred during the 3rd–8th week of pregnancy (OR = 1.8 (95% CI = 0.9–3.9) compared to those not exposed to any of the pesticide classes examined during the same time period. Small numbers prevent analysis of exposures occurring only in the same TRS.

Overall, the conclusions from our previous work remain unchanged. This corrected analysis shows a stronger association between fetal death due to congenital anomalies and residential proximity to applications of pyrethroids; risk was elevated four- to five-fold, depending on the definition of "non-exposed," when exposure occurred during the 3rd–8th week of pregnancy. Pyrethroids are often applied to crops in combination with other pesticides such as organophosphates and carbamates.[3–5] In our study, 90% of those exposed to pyrethroids were also exposed to these other pesticide classes. Thus, we did not have the power to examine whether the observed associations are the result of exposure to pyrethroids, other pesticides, or both.

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ERRATUM

In a recent article, "A case-control study of pesticides and fetal death due to congenital anomalies," by E.M. Bell, I. Hertz-Picciotto, J.J. Beaumont (Epidemiology 12:148–156, 2001) the categorization for pyrethroid pesticides was incorrect. The corrected pyrethroid category includes the following pesticides: permethrin, pyrethrin, cypermethrin, fenvalerate, and flucythrinate. The corrected odds ratios and 95% confidence intervals for the pyrethroid analyses in Tables 5 and 6 are presented here. The authors regret the error.

Further analysis using this revised categorization is discussed in a letter in this issue.

Corrections to Table 5 Adjusted* Odds Ratios and 95% CIs for Potential Exposure within the Same Location or Eight Surrounding Township, Range and Sections for Four Exposure Definitions

Exposure Definitions†	Pyrethroids		Adjusted	
	Control	Case	OR	CI
Exposure A				
No	535	56	2.2	1.0–4.7
Yes	76	17		
Exposure B				
No	556	60	2.2	1.0–4.7
Yes	55	13		
Exposure C				
No	579	61	3.8	1.6–9.1
Yes	32	12		
Exposure D				
No	343	30	4.9	1.9–12.9
Yes	32	12		

* All models adjusted for maternal age and county.
† Exposed to specified class versus not exposed to same class during:
Exposure A: the first 20 weeks gestation
Exposure B: the first 13 weeks gestation (first trimester)
Exposure C: the 3rd- to 8th-week period of gestation
Exposure D: exposed to specified class between 3 and 8 weeks gestation versus not exposed to any of the five classes during the 3rd- to 8th-week period of gestation.

Corrections to Table 6 Adjusted* Odds Ratios for Potential Exposure within the Same TRS for Four Exposure Definitions

Exposure Definitions†	Pyrethroids		Adjusted	
	Control	Case	OR	CI
Exposure A				
No	584	64	3.2	1.1–8.9
Yes	27	9		
Exposure B				
No	593	66	3.1	1.0–9.4
Yes	18	7		
Exposure C				
No	602	68		NR
Yes	9	5		
Exposure D				
No	547	58		NR
Yes	9	5		

NR = not reported because there were five or fewer exposed cases.
* All models adjusted for maternal age and county.
† Exposed to specified class versus not exposed to same class during:
Exposure A: the first 20 weeks gestation
Exposure B: the first 13 weeks gestation (first trimester)
Exposure C: the 3rd- to 8th-week period of gestation
Exposure D: exposed to specified class between 3 and 8 weeks gestation versus not exposed to any of the five classes during the 3rd- to 8th-week period of gestation.